The Ochsner Journal 9:220–226, 2009

Treatment of Refractory Angina

Mark A. Grise, MD, Anil Verma, MD, MPH

Department of Cardiology, Ochsner Clinic Foundation, New Orleans, LA

ABSTRACT

It is estimated that as many as 1,000,000 people in the United States have chronic symptomatic coronary artery disease (often referred to as refractory angina) that is recalcitrant to medical therapy and unamenable to conventional revascularization procedures. Patients have reproducible lifestyle-limiting symptoms of chest pain, shortness of breath, and easy fatigability. Several new therapies are available to treat this difficult patient population, including newer drugs, enhanced external counterpulsation, transmyocardial revascularization, and cell-based therapies. This article reviews the current state of the art for treatment of refractory angina.

INTRODUCTION

It is estimated that as many as 1,000,000 people in the United States have chronic symptomatic coronary artery disease (often referred to as refractory angina) that is recalcitrant to medical therapy and unamenable to conventional revascularization procedures. Patients have reproducible lifestyle-limiting symptoms of chest pain, shortness of breath, and easy fatigability. These symptoms are often due to totally occluded coronary arteries or diffuse coronary atherosclerosis that makes revascularization problematic. As our population ages and the incidence of diabetes mellitus increases, this clinical condition will become more prevalent. While there are conflicting data about long-term mortality, patients with this condition have significant morbidity and experience a lower quality of life.[1] Treatment modalities can be divided into 3 groups, namely, pharmacologic, noninvasive, and invasive therapies.

Address correspondence to:
Mark A. Grise, MD
Department of Cardiology
Ochsner Clinic Foundation
1514 Jefferson Highway
New Orleans, LA 70130
Tel: (504) 842-4135
Email: mgrise@ochsner.org

Key Words: Angina, angiogenesis, coronary artery disease, enhanced external counterpulsation, transmyocardial revascularization

CONVENTIONAL PHARMACOLOGIC THERAPIES

Oral Nitrates

Short-acting or long-acting oral nitrates are commonly used as antianginal agents. Nitrates provide anti-ischemic and antianginal effects by venodilatation and by reducing diastolic filling of the heart. There is also vasodilatation of the large epicardial coronary arteries and collateral vessels.[2] Tolerance to nitrates blunts the clinical effectiveness of short-acting nitrates and limits the use of nitrates as therapy for chronic angina. Treatment with long-acting nitrates should include a daily nitrate-free interval to preserve their clinical effectiveness. Long-acting nitrates in combination with β-blockers and calcium channel blockers produce greater antianginal and anti-ischemic effects in patients with stable angina.[3,4]

β-Blockers

β-Blockers decrease heart rate, myocardial contractility, and blood pressure, resulting in decreased myocardial oxygen demand. β-Blockers have been found to be efficacious in reducing morbidity and mortality in patients following myocardial infarction and in patients with chronic heart failure.[5] Selective β-1 agents are well tolerated and are preferable to nonselective agents. β-Blockers are also effective in controlling exercise-induced angina because they limit increases in heart rate.[6,7]

Calcium Channel Blockers

All calcium channel blockers exert a negative inotropic effect and dilate coronary and other arteries. The nondihydropyridine calcium channel blockers diltiazem and verapamil also reduce heart rate by slowing the sinus node or by decreasing ventricular response in patients with atrial flutter and fibrillation.[8] They also reduce the myocardial oxygen demand by lowering the systemic arterial pressure and by providing a negative inotropic effect. They are particularly effective in patients with vasospastic Prinzmetal angina.[9,10]

Dihydropyridine and nondihydropyridine agents have been shown to be equally efficacious as β-blockers in relieving angina and in improving exercise time to onset of angina or ischemia. In combination with β-blockers, they are effective in reducing angina symptoms.[11,12]

Antiplatelet Agents

Antiplatelet therapy, particularly aspirin, should be the cornerstone of any regimen in the management of atherosclerotic cardiovascular disease to prevent thrombotic cardiovascular events. Aspirin irreversibly inhibits cyclooxygenase and synthesis of platelet thromboxane A2. Aspirin reduces adverse cardiovascular events in patients with stable angina, including short-term and long-term risk of fatal and nonfatal myocardial infarction. It is recommended that, in the absence of contraindications, aspirin (75–325 mg daily) should be used routinely in all patients with acute and chronic ischemic heart disease.[13–16]

Clopidogrel bisulfate is a thienopyridine derivative that irreversibly inhibits the binding of adenosine diphosphate to its platelet receptors, thereby affecting adenosine diphosphate–dependent activation of the glycoprotein IIb-IIIa complex. The Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events trial[17] compared aspirin therapy with clopidogrel therapy in patients with previous myocardial infarction, stroke, and peripheral vascular disease. It demonstrated that clopidogrel was more effective than aspirin in decreasing the combined risk of myocardial infarction, vascular death, or ischemic stroke (absolute risk reduction, 0.51% per year; $P=.043$). Clopidogrel can be used in aspirin-intolerant patients, but its role in patients with chronic stable angina remains unknown.

Lipid-Lowering Agents

The pooled data from various investigations suggest that every 1% reduction in total cholesterol reduces coronary events by 2%.[18] Low-density lipoprotein cholesterol is an established risk marker for cardiovascular events.[19] Statin treatment reduces the risk of atherosclerotic cardiovascular complications in primary and secondary prevention. Statins also possess anti-inflammatory and antithrombotic effects. Current data and guidelines advocate that the target for low-density lipoprotein cholesterol should be less than 70 mg/dL (to convert cholesterol level to millimoles per liter, multiply by 0.0259) in patients with established coronary artery disease.[20]

NEWER PHARMACOLOGIC AGENTS

Ranolazine Hydrochloride

Ranolazine hydrochloride is a newer anti-ischemic agent approved in January 2006 by the US Food and Drug Administration for the treatment of chronic stable angina. Ranolazine is a partial fatty oxidation inhibitor and is believed to exert its effects via altering the transcellular late sodium current and modulating the sodium-dependent calcium channels during myocardial ischemia, which in turn inhibits the calcium overload that causes myocardial ischemia.[21] By inhibiting the increase in intracellular calcium, ranolazine decreases the left ventricular diastolic tension and improves myocardial perfusion.[22] It is also believed to facilitate energy production in hypoxic cardiomyocytes by partially shifting cardiac lipid oxidation to glucose oxidation.[23]

The Monotherapy Assessment of Ranolazine in Stable Angina trial[24] assessed the dose-response relationship of ranolazine and showed a significant dose-related improvement in the exercise tolerance among patients having angina treated with ranolazine vs placebo (Figure 1). Similarly, the Combination Assessment of Ranolazine in Stable Angina trial[25] demonstrated significant increases in exercise duration and time to electrographic ischemia during stress testing vs placebo when ranolazine was added to standard doses of atenolol, diltiazem, or amlodipine. Finally, the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes TIMI 36 trial[26] demonstrated a reduction in angina with ranolazine therapy and a favorable safety profile in a broad group of patients with angina.

L-Arginine

L-Arginine has been shown to increase coronary blood flow by improving endothelium-dependent vasodilation.[27] Treatment with oral L-arginine increases exercise duration and maximum workload during stress testing and decreases the time to onset of ST-segment depression.[28–30]

Nicorandil

Nicorandil is a nicotinamide ester that mimics nitrates in its activity, activates the mitochondrial adenosine triphosphate-sensitive potassium channels, and may offer ischemic preconditioning of the myocardium.[31] In the Impact of Nicorandil in Angina trial,[32] a total of 5,126 patients with stable angina were randomized to placebo or to nicorandil (20 mg twice daily). There were 398 (15.5%) primary end point events (nonfatal myocardial infarction, admission for cardiac chest pain, and death due to coronary heart disease) in the placebo group vs 337 (13.1%) in the nicorandil group ($P=.014$), representing a 17% relative risk reduction.

Ivabradine

Ivabradine is a pure heart rate-lowering agent that reduces myocardial oxygen demand without negative inotropic effects[33] and lowers heart rate at rest and

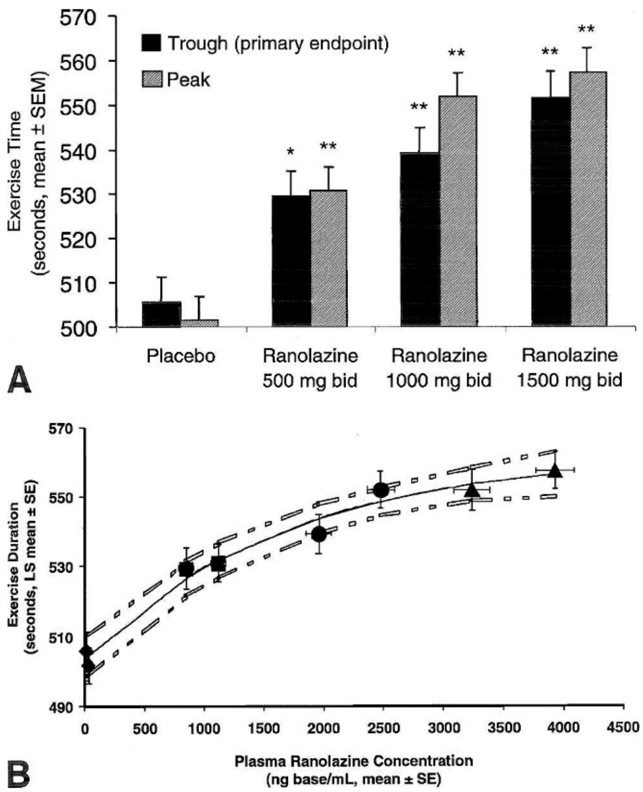

Figure 1. Symptom-limited exercise duration: dose and plasma concentration relationships. A. Exercise duration vs ranolazine hydrochloride dose. Data are shown at trough (solid bars [primary end point]) and peak (lined bars). Statistically significant increases were observed for each ranolazine dose vs placebo (*$P<.005$ vs placebo, **$P<.001$ vs placebo). A dose-response relationship was evident with greater increases at peak than at trough. Similar data were observed for time to onset of angina and time to 1-mm ST-segment depression. B. Exercise duration vs ranolazine plasma concentration. The mean exercise duration increases with the mean plasma ranolazine concentrations. From left to right, values for each treatment at trough and peak are represented by diamonds (placebo), squares (500 mg twice daily), circles (1,000 mg twice daily), and triangles (1,500 mg twice daily). Dotted lines represent the 95% confidence intervals around the fitted curve. (Reproduced with permission from Chaitman BR, Skettino SL, Parker JO, et al; MARISA Investigators. *J Am Coll Cardiol.* 2004;43(8):1375–1382.[24])

during exercise.[34] Ivabradine has demonstrated anti-ischemic and antianginal efficacy in randomized trials among patients having chronic stable angina pectoris compared with placebo as monotherapy[34] or when combined with atenolol.[35,36]

NONINVASIVE THERAPIES

Enhanced External Counterpulsation

Enhanced external counterpulsation (EECP) therapy represents a noninvasive technique for which a reduction of angina symptoms, an improvement in objective measures of myocardial ischemia, and an increase in left ventricular function (systolic and diastolic) have been shown.[37] Precise timed diastolic pressure augmentation is achieved by electrocardiogram-gated rapid sequential compression of the lower extremities during diastole, followed by decompression during systole. Inflatable cuffs are applied on the calves, the lower and upper thighs, and the buttocks, sequentially compressing the lower limbs during diastole (Figure 2) and rapidly deflating before systole.[38] A typical treatment course consists of 35 outpatient treatments administered 1 hour per day over 7 weeks.

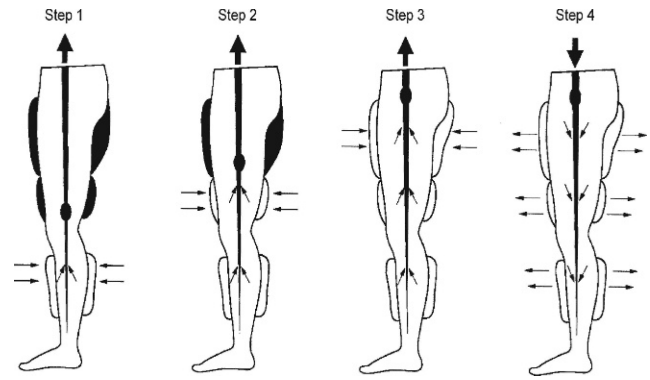

Figure 2. Technique of enhanced external counterpulsation. (Reproduced with permission from Manchanda A, Soran O. *J Am Coll Cardiol.* 2007;50(16):1523–1531.[38])

The Multicenter Study of Enhanced External Counterpulsation[39] assessed the efficacy of EECP in patients with chronic stable angina and positive exercise stress test results who were randomized to hemodynamically inactive counterpulsation vs active counterpulsation. Active counterpulsation patients experienced fewer anginal episodes compared with inactive counterpulsation patients ($P<.05$).

The mechanism of the sustained antianginal benefit with EECP remains unclear. Proposed mechanisms include increased coronary perfusion pressure and improved endothelial function. The therapy may also promote myocardial collateralization via recruitment of preformed collateral vessels. The process of arteriogenesis and angiogenesis may also have a role (Figure 3).

In the Multicenter Study of Enhanced External Counterpulsation,[39] 55% of patients in the active counterpulsation arm reported adverse events (such as lower limb bruise, edema, and leg pain), but only 10% of adverse events were severe enough to prompt withdrawal. Therapy using EECP is contraindicated in patients with moderate to severe aortic insufficiency, uncontrolled arrhythmias, coagulopathy, severe hypertension, decompensated heart failure,

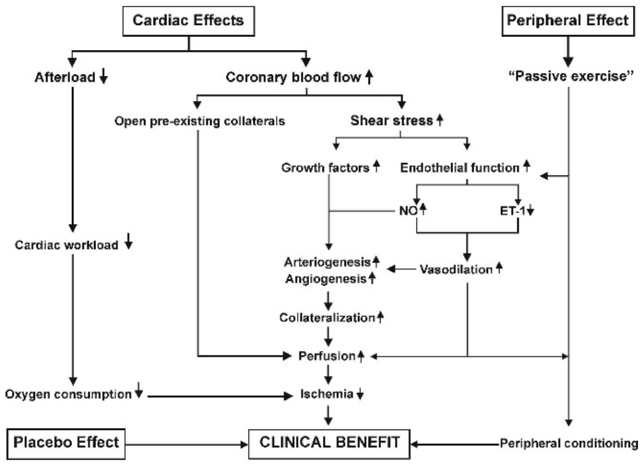

Figure 3. Possible mechanisms responsible for the clinical benefit associated with enhanced external counterpulsation therapy. (Reproduced with permission from Manchanda A, Soran O. *J Am Coll Cardiol.* 2007;50(16):1523–1531.[38])

and severe peripheral vascular disease, including venous disease, aortic aneurysm, and severe chronic obstructive pulmonary disease, as well as during pregnancy.[39]

INVASIVE THERAPIES

Transmyocardial Revascularization

Transmyocardial revascularization (TMR) is based on the use of high-power lasers that create transmural channels with a 1-mm diameter.[40] These channels are created along the free left ventricular wall and are placed 1 cm apart in the ischemic myocardium in conjunction with coronary artery bypass grafting or as stand-alone therapy. The precise mechanism for its efficacy is not entirely understood. Initially, it was thought that the channels provided direct blood flow to the myocardium; however, these channels have been shown to close within weeks after the procedure. It is now believed that TMR stimulates angiogenesis or leads to denervation of the myocardium.[41,42]

Several trials have evaluated TMR in ''no-option'' patients. Five prospective randomized trials with 1-year follow-up have demonstrated that TMR is associated with better angina relief, improved exercise tolerance, decreased hospitalization, and longer event-free survival compared with maximal medical therapy.[43–47] Allen et al[43] reported on a 5-year follow-up of patients treated with TMR vs medical therapy. They demonstrated significantly increased Kaplan-Meier survival estimates in patients randomized to TMR (65% vs 52%, P=.05). The significant angina relief previously observed at the 12-month follow-up in those patients treated with TMR therapy was sustained at longer follow-up. A significant reduction in the mean (SD) Canadian Cardiovascular Society angina class from baseline (4.0 [0.0]) was observed in surviving patients at 3 months (1.4 [1.3]), 6 months (1.3 [1.2]), 1 year (1.5 [1.4]), and 5 years (1.2 [1.1]) after therapy with TMR (P=.0001 for all). With a mean follow-up of 5 years, significantly more patients treated with TMR experienced 2 or more Canadian Cardiovascular Society class improvements from baseline (88% [42 of 48] vs 44% [16 of 36], P=.001). In a follow-up study by Allen et al,[48] more patients treated with TMR were angina free at 5 years (33% [16 of 48] vs 11% [4 of 36], P=.02).

The US Food and Drug Administration has approved a device (Pearl 5.0; Cardiogenesis Corporation, Irvine, CA) that allows for minimally invasive robot-assisted TMR to be performed endoscopically. This should allow for a less morbid procedure with quicker recovery time in these patients who often have multiple medical comorbidities.[49]

Angiogenesis

The potential to grow new blood vessels has been evaluated for decades. Protein factors and gene therapies have been evaluated in randomized clinical trials. While these trials have demonstrated acceptable safety outcomes, efficacy has been only modest with respect to angina and quality-of-life end points.[50,51] Therefore, there is an interest in cell-based therapies to treat chronic ischemic heart disease.[52]

Using bone marrow cells to treat patients with chronic ischemic heart disease is under intense investigation. Results of animal studies[53,54] suggest that bone marrow cell therapy may improve myocardial perfusion and increase left ventricular function in chronic coronary ischemia. Several small randomized trials have evaluated cell-based therapies in these patients.[55–58] Tse et al[57] reported on the effect of intramyocardial injection of bone marrow cells in patients with chronic ischemic heart disease. Clinical outcomes, myocardial perfusion, and left ventricular function were assessed in 19 patients who received bone marrow cells and in 9 patients who received placebo. Bone marrow cell injection was associated with a modest increase in exercise capacity and in left ventricular function. However, there was no difference in myocardial perfusion between the 2 groups in a follow-up study.[59] van Ramshorst et al[60] published their results of 50 patients with chronic myocardial ischemia who were randomized to intramyocardial injection of 100×10^6 autologous bone marrow-derived mononuclear cells or a placebo solution. They demonstrated a statistically significant but modest improvement in myocardial perfusion among patients who received bone marrow cells. Modest improvements were noted in Canadian Cardiovascular Society class, quality-of-life score, and exercise capacity

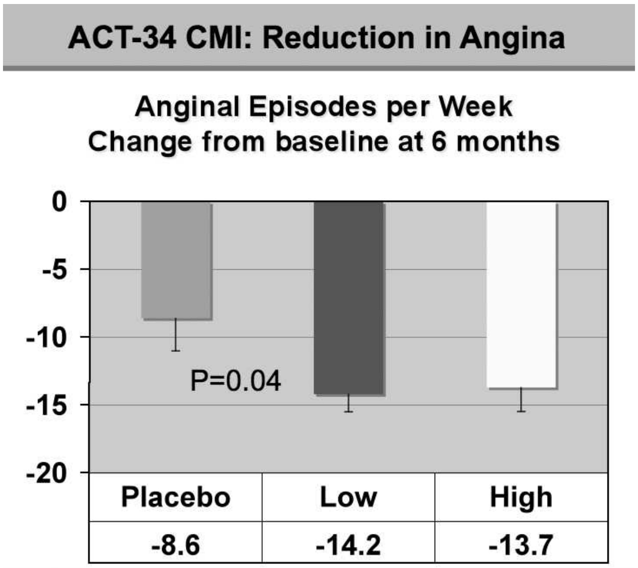

Figure 4. Change in anginal episodes per week from baseline to 6 months. (Reproduced with permission from Losordo D. Paper presented at: 68th Annual Scientific Session of the American College of Cardiology; March 28, 2009; Orlando, FL.[61])

among treated patients. Losordo[61] presented the results of a phase II study evaluating 167 no-option patients randomized to intramyocardial injection of placebo (n=56) or to 1 of 2 doses of bone marrow cells (1×10^5 $CD34^+$ cells per kilogram [n=55] or 5×10^5 $CD34^+$ cells per kilogram [n=56]). At the 12-month follow-up, the prespecified Poisson regression with extravariability analysis failed to find a significant

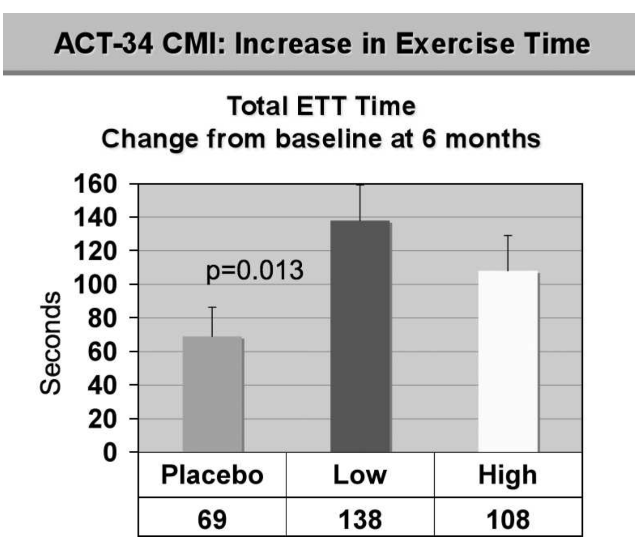

Figure 5. Total Exercise Tolerance Test Time change from baseline to 6 months. (Reproduced with permission from Losordo D. Paper presented at: 68th Annual Scientific Session of the American College of Cardiology; March 28, 2009; Orlando, FL.[61])

Major Adverse Cardiac Events (12 Months)

	Control	1×10^5	5×10^5	p-value
Any MACE	25.0%	12.7%	14.3%	0.194
Death, MI, Urgent Revasc	10.7%	7.3%	5.4%	0.594
Death, MI, Post-PCI MI, Urgent Revasc	12.5%	7.3%	5.4%	0.416
Any MI	7.1%	9.1%	5.4%	.707
MI pre/injection	3.6%	1.8%	1.8%	1.000
Death, MI, Urgent Revasc, Worse CHF, ACS	21.4%	9.1%	8.9%	0.123

Figure 6. Major adverse cardiac events at 12 months. (Reproduced with permission from Losordo D. Paper presented at: 68th Annual Scientific Session of the American College of Cardiology; March 28, 2009; Orlando, FL.[61])

reduction in the number of anginal episodes per week. However, when calculated by analysis of variance, the weekly angina frequency was significantly lower with treatment ($P=.04$) (Figure 4). The total increase in exercise time also significantly improved with treatment (Figure 5). The more robust benefit was seen in the lower-dose group. Also, there was a trend toward fewer major adverse cardiac events in the treated groups (Figure 6).

Although the early results of cell-based therapies are promising, numerous issues remain unresolved. The specific type of cells, the amount of cells delivered, and the route of cell delivery (intramyocardial, combined with TMR, or intracoronary) that will be most efficacious are as yet unknown. While most studies have demonstrated acceptable short-term safety, the long-term effect of cell delivery to the myocardium is unknown.

CONCLUSION

Refractory angina is a challenging clinical condition that is increasing in prevalence. Patients experience significant morbidity, despite traditional revascularization procedures and maximal medical therapy. Treatment is directed at instituting therapies known to decrease mortality (revascularization, antiplatelet therapy, lipid reduction, and β-blockers) and to improve symptoms. Novel approaches are available to patients who remain symptomatic despite standard therapies. These include newer drugs, EECP, TMR, and the potential for cell-based and gene therapies. Future studies will better define which patients will most benefit from these therapies.

REFERENCES

1. Yang EH, Barsness GW, Gersh BJ, Chandrasekaran K, Lerman A. Current and future treatment strategies for refractory angina. *Mayo Clinic Proc*. 2004;79(10):1284–1292.

2. Kaski JC, Plaza LR, Meran DO, Araujo L, Chierchia S, Maseri A. Improved coronary supply: prevailing mechanism of action of nitrates in chronic stable angina. *Am Heart J*. 1985;110(1, pt 2): 238–245.
3. Akhras F, Jackson G. Efficacy of nifedipine and isosorbide mononitrate in combination with atenolol in stable angina. *Lancet*. 1991;338(8774):1036–1039.
4. Schneider W, Maul FD, Bussmann WD, Lang E, Hor G, Kaltenbach M. Comparison of the antianginal efficacy of isosorbide dinitrate (ISDN) 40 mg and verapamil 120 mg three times daily in the acute trial and following two-week treatment. *Eur Heart J*. 1988;9(2):149–158.
5. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease, I: treatments following myocardial infarction. *JAMA*. 1988;260(14):2088–2093.
6. Packer M, Bristow MR, Cohn JN, et al; U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334(21):1349–1355.
7. Capone P, Mayol R. Celiprolol in the treatment of exercise induced angina pectoris. *J Cardiovasc Pharmacol*. 1986;8(suppl 4): S135–S137.
8. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. *Drugs*. 1996;51(5):792–819.
9. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina) [published corrections appear in *J Am Coll Cardiol*. 1999;34(1):314 and *J Am Coll Cardiol*. 2001;38(1):296]. *J Am Coll Cardiol*. 1999;33(7):2092–2197.
10. Antman E, Muller J, Goldberg S, et al. Nifedipine therapy for coronary-artery spasm: experience in 127 patients. *N Engl J Med*. 1980;302(23):1269–1273.
11. Savonitto S, Ardissiono D, Egstrup K, et al. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris: results of the International Multicenter Angina Exercise (IMAGE) Study. *J Am Coll Cardiol*. 1996;27(2):311–316.
12. Foale RA. Atenolol versus the fixed combination of atenolol and nifedipine in stable angina pectoris. *Eur Heart J*. 1993;14(10):1369–1374.
13. Patrono C, Coller B, FitzGerald GA, Hirsh J, Roth G. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3)(suppl):234S–264S.
14. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients [published correction appears in *BMJ*. 2002;324(7330):141]. *BMJ*. 2002;324(7329):71–86.
15. Ridker PM, Manson JE, Gaziano JM, Buring JE, Hennekens CH. Low-dose aspirin therapy for chronic stable angina: a randomized, placebo-controlled clinical trial. *Ann Intern Med*. 1991;114(10):835–839.
16. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1983;309(7):396–403.
17. CAPRIE Steering Committee. A randomised, blinded, trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). *Lancet*. 1996;348(9038):1329–1339.
18. LaRosa JC, Hunninghake D, Bush D, et al; Task Force on Cholesterol Issues, American Heart Association. The cholesterol facts: a summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease: a joint statement by the American Heart Association and the National Heart, Lung, and Blood Institute. *Circulation*. 1990;81(5):1721–1733.
19. Lavie CJ, Milani RV, O'Keefe JH. Statin wars: emphasis on potency vs event reduction and safety? *Mayo Clin Proc*. 2007;82(5):539–542.
20. O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dL: lower is better and physiologically normal. *J Am Coll Cardiol*. 2004;43(11):2142–2146.
21. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation*. 2004;110(8):904–910.
22. Belardinelli L, Shryock JC, Fraser H. Inhibition of the late sodium current as a potential cardioprotective principle: effects of the late sodium current inhibitor ranolazine. *Heart*. 2006;92(suppl 4):iv6–iv14.
23. McCormack JG, Barr RL, Wolff AA, Lopaschuk GD. Ranolazine stimulates glucose oxidation in normoxic, ischemic, and reperfused ischemic rat hearts. *Circulation*. 1996;93(1):135–142.
24. Chaitman BR, Skettino SL, Parker JO, et al; MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43(8):1375–1382.
25. Chaitman BR, Pepine CJ, Parker JO; Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004;291(3):309–316.
26. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al; MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular events in patients with non–ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA*. 2007;297(16):1775–1783.
27. Egashira K, Hirooka Y, Kuga T, Mohri M, Takeshita A. Effects of L-arginine supplementation on endothelium-dependent coronary vasodilation in patients with angina pectoris and normal coronary arteriograms. *Circulation*. 1996;94(2):130–134.
28. Ceremużyński L, Chamiec T, Herbaczyńska-Cedro K. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. *Am J Cardiol*. 1997;80(3):331–333.
29. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. *Cochrane Database Syst Rev*. 2005;(4):CD003614.
30. Lee L, Horowitz J, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. *Eur Heart J*. 2004;25(8):634–641.
31. Markham A, Plosker GL, Goa KL. Nicorandil: an updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs*. 2000;60(4):955–974.
32. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact of Nicorandil in Angina

(IONA) randomised trial [published correction appears in *Lancet*. 2002;360(9335):806]. *Lancet*. 2002;359(9314):1269–1275.

33. DiFrancesco D. Funny channels in the control of cardiac rhythm and mode of action of selective blockers. *Pharmacol Res*. 2006;53(5):399–406.
34. Borer JS, Fox K, Jaillon P, Lerebours G; Ivabradine Investigators Group. Antianginal and antiischemic effects of ivabradine, an I_f inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation*. 2003;107(6):817–823.
35. Tardif JC, Ponikowski P, Kahan T; ASSOCIATE Study Investigators. Efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J*. 2009;30(5):540–548.
36. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K; INITIATIVE Investigators. Efficacy of ivabradine, a new selective I_f inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005;26(23):2529–2536.
37. Urano H, Ikeda H, Ueno T, Matsumoto T, Murohara T, Imaizumi T. Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. *J Am Coll Cardiol*. 2001;37(1):93–99.
38. Manchanda A, Soran O. Enhanced external counterpulsation and future directions: step beyond medical management for patients with angina and heart failure [published correction appears in *J Am Coll Cardiol*. 2007;50(25):2441]. *J Am Coll Cardiol*. 2007;50(16):1523–1531.
39. Arora RR, Chou TM, Jain D, et al. The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol*. 1999;33(7):1833–1840.
40. Mirhoseini M, Cayton MM. Revascularization of the heart by laser. *J Microsurg*. 1981;2(4):253–260.
41. Gassler N, Wintzer HO, Stubbe HM, Wullbrand A, Helmchen U. Transmyocardial laser revascularization: histological features in human nonresponder myocardium. *Circulation*. 1997;95(2):371–375.
42. Sundt TM III, Kwong KF. Clinical experience with the holmium:YAG laser for transmyocardial laser revascularization and myocardial denervation as a mechanism. *Semin Thorac Cardiovasc Surg*. 1999;11(1):19–23.
43. Allen KB, Dowling RD, Fudge TL, et al. Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina. *N Engl J Med*. 1999;341(14):1029–1036.
44. Aaberge L, Nordstrand K, Dragsund M, et al. Transmyocardial revascularization with CO_2 laser in patients with refractory angina pectoris: clinical results from the Norwegian Randomized Trial. *J Am Coll Cardiol*. 2000;35(5):1170–1177.
45. Burkhoff D, Schmidt S, Schulman SP, et al; ATLANTIC Investigators (Angina Treatments–Lasers and Normal Therapies in Comparison). Transmyocardial revascularisation compared with continued medical therapy for treatment of refractory angina pectoris: a prospective randomised trial. *Lancet*. 1999;354(9182):885–890.
46. Frazier OH, March RJ, Horvath KA. Transmyocardial revascularization with a carbon dioxide laser in patients with end-stage coronary artery disease. *N Engl J Med*. 1999;341(14):1021–1028.
47. Schofield PM, Sharples LD, Caine N, et al. Transmyocardial laser revascularisation in patients with refractory angina: a randomised controlled trial [published correction appears in *Lancet*. 1999;353(9165):1714]. *Lancet*. 1999;353(9152):519–524.
48. Allen KB, Dowling RD, Angell WW, et al. Transmyocardial revascularization: 5-year follow-up of a prospective, randomized multicenter trial. *Ann Thorac Surg*. 2004;77(4):1228–1234.
49. Wehberg KE, Todd JC, Julian JS, Ogburn NL, Klopp EH, Buchness MP. Robotic-assisted off-pump sole transmyocardial revascularization: case report. *Heart Surg Forum*. 2004;7(2):E130–E131.
50. Henry TD. Can we really grow new blood vessels? *Lancet*. 1998;351(9119):1826–1827.
51. Simons M. Angiogenesis: where do we stand now? *Circulation*. 2005;111(12):1556–1566.
52. Henry TD, Satan D. Therapeutic angiogenesis. In: Barsness G, Holmes DR Jr, et al. *Coronary Artery Disease: New Approaches Without Traditional Revascularization*. New York: Springer.In press.
53. Fuchs S, Baffour R, Zhou YF, et al. Transendocardial delivery of autologous bone marrow enhances collateral perfusion and regional function in pigs with chronic experimental myocardial ischemia. *J Am Coll Cardiol*. 2001;37(6):1726–1732.
54. Silva GV, Litovsky S, Assad JA, et al. Mesenchymal stem cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a canine chronic ischemia model. *Circulation*. 2005;111(2):150–156.
55. Beeres SL, Bax JJ, Dibbets P, et al. Effect of intramyocardial injection of autologous bone marrow–derived mononuclear cells on perfusion, function, and viability in patients with drug-refractory chronic ischemia. *J Nucl Med*. 2006;47(4):574–580.
56. Fuchs S, Kornowski R, Weisz G, et al. Safety and feasibility of transendocardial autologous bone marrow cell transplantation in patients with advanced heart disease. *Am J Cardiol*. 2006;97(6):823–829.
57. Tse HF, Kwong YL, Chan JK, Lo G, Ho CL, Lau CP. Angiogenesis in ischaemic myocardium by intramyocardial autologous bone marrow mononuclear cell implantation. *Lancet*. 2003;361(9351):47–49.
58. Briguori C, Reimers B, Sarais C, et al. Direct intramyocardial percutaneous delivery of autologous bone marrow in patients with refractory myocardial angina. *Am Heart J*. 2006;151(3):674–680.
59. Tse HF, Thambar S, Kwong YL, et al. Prospective Randomized Trial of Direct Endomyocardial Implantation of Bone Marrow Cells for Treatment of Severe Coronary Artery Diseases (PROTECT-CAD trial). *Eur Heart J*. 2007;28(24):2998–3005.
60. van Ramshorst J, Bax JJ, Beeres SL, et al. Intramyocardial bone marrow cell injection for chronic myocardial ischemia: a randomized controlled trial. *JAMA*. 2009;301(19):1997–2004.
61. Losordo D. Randomized, double-blind placebo controlled phase 2 study of intramyocardial injection of autologous $CD34^+$ cells for treatment of refractory angina. Paper presented at: 68th Annual Scientific Session of the American College of Cardiology; March 28, 2009; Orlando, FL.